

## **REMARKS**

This Amendment accompanies a Request for Continued Examination (RCE). Claims 1-20 are pending with claims 6, 9 and 15-17 withdrawn from consideration as being directed to a non-elected species. Accordingly, claims 1-5, 7-8, 10-14 and 18-20 are under examination. Claims 1, 3-5, 12-14 and 18-20 have been amended. Support for the amendments can be found throughout the application as filed. Support for the amendment to claim 1 reciting at least one bioengineering objective can be found, for example, in claim 19 as filed. Support for the amendment reciting that the claimed bioengineering objectives and cellular objectives are objective functions can be found at, for example, paragraph 0042. Accordingly, the amendments do not raise an issue of new matter and entry thereof is respectfully requested. Applicants have reviewed the Advisory Action mailed August 28, 2007, and respectfully traverse all grounds of rejection for the reasons that follow.

### **Priority**

The Examiner maintains that provisional application serial number 60/395,763, filed July 10, 2002, (the '763 application) fails to provide adequate support or enablement for claims 1-5, 7-8, 10-14 and 18-20. The Examiner acknowledges that the '763 application recites that a computational framework is developed and alludes to an MILP-based formulation, but concludes that such teachings and descriptions fail to provide adequate enablement and written description to one of ordinary skill in the art.

Applicants respectfully point out that the Examiner has not provided any reason why such descriptions fail to provide sufficient teachings and support for the invention as claimed. Applicants further draw the Examiner's attention that the standard is not "one of ordinary skill" (Advisory Action, continuation sheet, para. 1). Rather, the first paragraph of § 112 requires that the teachings and support be sufficient for a person skilled in the art. The '763 application states that the MILP-based formulations were developed based on "the same duality theory concepts applied to metabolic objective function determination formulation" (Response filed August 16, 2007, page 5, para. 3). Such description is sufficient support and enablement to one skilled in the art because the referenced duality theory concepts were well known to those skilled in the art. Following the teachings and guidance in the application those skilled in the art would have understood how to couple at least one bioengineering objective with at least one cellular

objective applying well known duality theory concepts to an objective function determination formulation. Therefore, Applicants respectfully maintain that the requirements of 35 U.S.C. § 112, first paragraph, are satisfied.

#### **Rejections Under 35 U.S.C. § 112, First Paragraph**

Claim 1 stands rejected under 35 U.S.C. § 112, first paragraph, for lacking enablement allegedly because the claim is directed to any optimization problem, but that the specification enables only linear optimization. The Examiner appears to allege that Applicants argument that the claims are directed only to optimization methods that can be formulated to couple the two claimed objective functions is unpersuasive because the claims include more than two objectives. The Examiner further maintains that the convex basis methods of Papin et al. support lack of enablement for methods other than linear optimization allegedly because they analyze systems of inequalities in determining elementary modes which read on an optimization problem.

Regarding the assertion that Applicants argued coupling only two objective functions, Applicants respectively point out that the claims recite the open-ended transition term “comprising.” Therefore, recitation of a method comprising a bioengineering objective is construed to mean one or more bioengineering objectives. Although clear as claimed and as argued of record, Applicants have amended the claims to explicitly recite at least one bioengineering objective function. Applicants respectfully submit that this ground of rejection is moot.

With respect to the citation of Papin et al., Applicants respectfully maintain that the convex basis methods described therein are distinct from, and non-analogous to, an optimization problem because convex analysis does not formulate an objective function and solve for its maximization or minimization. Determining maximum theoretical yield of a particular product does not constitute maximization or minimization of an objective function because it is a result of the convex analysis, not an objective function to be solved for in an optimization problem. Nevertheless, the claims now recite forming a linear optimization problem. In light of this amendment, Applicants respectfully submit that this ground of rejection is moot and its withdrawal is respectfully requested.

### **Rejections Under 35 U.S.C. § 103**

Claims 1-5, 7-8, 10-14 and 18-20 stand rejected under 35 U.S.C. § 103(a) for allegedly being obvious over Burgard et al., *Biotechnology and Bioengineering* 74:364-375 (2001), in view of Yang et al., *Metabolic Engineering* 1:26-34 (1999) and further in view of Voit, *Biotechnology and Bioengineering* 40:572-82 (1992).

The Examiner bears the burden of establishing a *prima facie* case of obviousness. *In re Rijckaert*, 9 F.3 1531, 1532, (Fed. Cir. 1993). Only if this burden is met does the burden of coming forward with rebuttal argument or evidence shift to the applicant. *Id.* at 1532. When the references cited by the Examiner fail to establish a *prima facie* case of obviousness, the rejection is improper and will be overturned. *In re Fine*, 837 f.2d 1071, 1074 (Fed. Cir. 1988).

In maintaining the above ground of rejection, the Examiner asserts that Applicants' arguments are unpersuasive for the reasons of record. However, the Examiner appears not to address Applicants arguments filed August 16, 2007. Mere reiteration of the initial rejection is insufficient to satisfy the Examiner's burden when a rebuttal has been made to that rejection. Applicants' previous responses have shown that the passage cited by the Examiner does not refer to a cellular objective function of an optimization problem. However, no reason explaining why this distinction is unpersuasive has been provided. Should this ground of rejection be maintained, Applicants respectfully request that the Examiner particularly point out why the cited passage in Burgard et al. in the abstract, lines 4-14, teaches or suggests a cellular objective function of an optimization problem.

The Examiner further alleges that Applicants argued the references separately. Applicants' respectfully point out that their earlier response, filed December 19, 2006, argued the cited combination. Applicants response filed August 16, 2007, particularly addressed the issue narrowed by the earlier prosecution. Namely, that Burgard et al. fail to teach or suggest coupling at least one cellular objective with at least one bioengineering objective (see, e.g., Office Action mailed February 16, 2007, at page 9, para. 4 through page 10, para. 1).

Applicants pointed out that the support relied on by the Examiner does not constitute coupling at least one bioengineering objective with a least one cellular objective in an optimization problem as claimed by the invention. No reason has been provided why testing "the effect of gene deletions on biomass production and addressing the maximum theoretical production of the 20 amino acids for aerobic growth" (*Id.* at p.10) teaches or suggests coupling at

least one bioengineering objective function with at least one cellular objective function in light of Applicants showing that, for example, the referenced aerobic growth conditions does not constitute an objective function to an optimization problem. The cited passage also fails to teach or suggest the coupling of the claimed objective functions. Applicants respectfully submit that it does not. Applicants have amended the claims to recite at least one bioengineering objective function and at least one cellular objective function to more explicitly point out that the claimed objectives are objective functions of an optimization problem as compared to a characteristic or to growth conditions. Should this ground of rejection be maintained, Applicants respectfully request that the Examiner particularly point out why Applicants remarks are deemed unpersuasive. The mere statement that it does after a rebuttal by Applicant is insufficient to satisfy the Examiner's burden.

The Advisory Action summarizes the original rejection by reasserting that Voit et al. describe a bilevel optimization problem to optimize the yield of a bioengineering objective while maintaining the cellular objective at steady state. Burgard et al. allegedly describes solving an optimization problem to maximize the production of the 20 amino acids and maintaining growth on glucose and acetate.

This summary appears to confirm that the cited references fail to teach or suggest the claimed invention because it concedes that neither Burgard et al. or Voit et al. teach or suggest coupling at least one bioengineering objective with at least one cellular objective. In particular, the Advisory Action states:

Voit et al. teach the application of linear programming optimization methods and show a bilevel optimization problem to optimize the yield of the bioengineering objective while maintaining the cellular objective of steady state.

*Id.*, continuation sheet, para. 3 (emphasis added).

As described previously with reference to aerobic conditions, mere mention of a cellular characteristic does not constitute a cellular objective function as claimed because, without more, it is not formulated as an objective function of an optimization problem. The act of "maintaining" something is contrary to the act of "optimizing" because the former term refers to restricting the kinetics within a set boundaries while the later term refers to altering the kinetics until they achieve the most desirable or favorable result. Moreover, Voit et al. explicitly teach

away from coupling a at least one bioengineering objective with at least one cellular objective when he states:

Consequently, maximization becomes very complicated because the steady-state constraints and objective functions are nonlinear and difficult to evaluate. An exception is the formulation of integrated biochemical systems with S-system differential equations. These equations are nonlinear but become linear when restricted to steady state.

*Id.*, page 373, col. 1, para. 4, line 10 through col. 2, para. 1., line 4 (emphasis added).

Restricting equations to steady state teaches away from optimization of this characteristic as a cellular objective because this restriction is employed to confer linearity onto S-system differential equations – not to optimize steady state kinetics. Accordingly, the alleged bilevel optimization of Voit et al. cannot suggest or provide the requisite motivation for coupling and optimization of an objective functions as claimed.

Similarly, the Advisory Action further states that Burgard et al. show “solving an optimization problem to maximize the production of the 20 amino acids and maintaining growth on glucose and acetate.” *Id.*, continuing sheet, para. 3 (emphasis added). As described above, maintaining growth does not teach or suggest optimizing growth nor does it teach or suggest that this characteristic is formulated as an objective function to a computational optimization problem.

Yang et al. is directed to metabolic flux analysis and describe a strain having a deleted acetate kinase (ACK) and a deleted acetyl phosphotransferase (PTA) shows reduced acetate production at the expense of growth rate (abstract). Therefore, Yang et al. does not provide that which is missing from Burgard et al. and Voit et al. because it fails to teach or suggest optimizing a cellular objective as an objective function nor does is teach or suggest coupling the claimed at least one bioengineering objective with at least one cellular objective.

In addition, the requisite motivation to combine also is lacking in the cited combination of references. In the Office Action mailed February 16, 2007, the Examiner states:

Burgard et al. motivate one to combine metabolic modeling to produce pathways with enhanced production. Voit motivates one to combine through the teach [*sic*] that as reliable kinetic information regarding biochemical pathways and networks of medical and industrial interest grow, the information can be used to optimize the pathways and networks to achieve goals of interest, such as simulating a bacterium to produce unnaturally high

amounts of oxychemcials. Yang et al. motivates one combine [sic] using the specific example of reduction of acetate production in *E. coli*.

*Id.*, at page 11.

Applicants respectfully submit that nothing in the cited rationale “identify[s] a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does” (*KSR Int’l. Co. v. Teleflex, Inc., et al.*, 127 S. Ct. 1727, 1741 (2007)) because there is no hint as to coupling at least one bioengineering objective function with at least one cellular objective function as claimed. Metabolic modeling to produce pathways with enhanced production lacks any reason that would prompt one of ordinary skill to couple at least one bioengineering objective with at least one cellular objective. Use of reliable information to optimize pathways also lacks any reason that would have prompted one of ordinary skill to couple at least one bioengineering objective with at least one cellular objective. Reduction in acetate production because of a gene mutation similarly fails to provide a reason that would have prompted a person of ordinary skill to couple at least one bioengineering objective with at least one cellular objective. Applicants respectfully submit that none exists.

Because all of the cited references fail to teach or suggest coupling at least one bioengineering objective with at least one cellular objective, and because Voit et al. teach away from optimizing a characteristic in his optimization method, one of ordinary skill would not have combined the optimization method of Voit et al. in the method of Burgard et al. to develop a strain of *E. coli* that overproduces lactate as allegedly described by Yang et al. Therefore, Applicants respectfully maintain that the cited combination of references do not render the claimed obvious.

## **CONCLUSION**

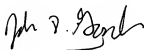
In light of the Amendments and Remarks herein, Applicant submits that the claims are in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he is invited to call the undersigned attorney.

Please consider this a Request for a One-Month Extension of Time from October 16, 2007 to November 16, 2007 and charge Deposit Account No. 26-0084 the amount of \$60.00 for this extension.

This amendment accompanies the filing of a Request for Continued Examination (RCE). Please charge Deposit Account No. 26-0084 the amount of \$405.00 for the RCE per the attached transmittal. No other fees or extensions of time are believed to be due in connection with this amendment; however, consider this a request for any extension inadvertently omitted, and charge any additional fees to Deposit Account No. 26-0084.

Reconsideration and allowance is respectfully requested.

Respectfully submitted,



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